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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/830,190	04/21/2004	Ananth Annapragada	27428-4	7714

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EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
10/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

bkern@kerniplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/830,190	ANNAPRAGADA ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This is a reopening after the decision by the BPAI mailed on 9/14/09 which adapts a new grounds of rejection based on newly found prior art. The reopening has TC director approval as indicated by the signature hereinbelow.

/Michael G. Wityshyn/
Acting Director, Technology Center 1600

Claims and Previous Rejections Status

2. Claims 1-4,6-11 and 25-33 are pending in the application.

3. The rejection of claims 1-4,6-11 and 25-33 under 35 U.S.C. 103(a) as being unpatentable over Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) in view of Payne et al. (US 4,744,989) and further in view of Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) or Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) is withdrawn due to the decision by the BPAI.

New Grounds of Rejection/Objection

Claim Objections

4. Claims 27 and 33 are objected to because of the following informalities: the instant claims recite, DSPE-MPEG2000 as corresponding to [N-(carbonylmethoxypolyethyleneglycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphatidylcholine]". DSPE corresponds to1,2-distearoyl-sn-glycerol-3-phosphoethanolamine. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 27 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if DSPE-MPEG2000 or [N-(carbonylmethoxypolyethyleneglycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphatidylcholine] is the required lipid/phospholipid. The instant claims recite, DSPE-MPEG2000 as corresponding to [N-(carbonylmethoxypolyethyleneglycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphatidylcholine]". DSPE corresponds to1,2-distearoyl-sn-glycerol-3-phosphoethanolamine.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1,6-8,10,25 and 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. (US 6,468,5050B1).

9. Lang et al. (US 6,468,5050B1) teaches of liposomes composed of egg phosphatidylcholine, cholesterol and polyethylene glycol derivatized phosphatidylethanolamine [PEG-PE, i.e. N-(w-methoxypoly(oxyethylene)-α-carbonyl)-

1,2-distearyl-3-SH-phosphatidylethanolamine (DSPE)]. The liposomes encapsulate Gd-DTPA-BMA (a nonradioactive contrast agent) and the nonencapsulated materials were removed using sephadex G-50 gel-exclusion chromatography. The liposomes are of the sizes of about 150 nm, 135 nm or 110 nm in mean diameter, are not autoclaved and provided a maximum tumor enhancement after 24 hours. (See abstract; column 5, Examples, General Materials and Methods, Preparation of Sterically Stabilized Liposomes Carrying Gd-Chelates for Magnetic Resonance Imaging; figures 1 and 2; column 2, lines 40-49; column 10, lines 37-56). The liposomes of the disclosure can be administered using an intravenous syringe injection, catheter, etc. (column 4, lines 8-22).

The liposomes of the disclosure have all of the same constituents (a phospholipid, cholesterol, a phospholipid derivatized with a polymer chain and a nonradioactive contrast-enhancing agent) and are the same size as the liposomes of the instant claims. Therefore, the liposomes of the disclosure anticipate the liposomes of the instant claims, have the same properties and are capable of the same functions, such as enhancing contrast of one or more areas of a subject for X-ray imaging. It is noted that the recitation of "for enhancing contrast of one or more areas of a subject for X-ray imaging when administered", is a recitation of the intended use of the claimed invention and must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

10. Claims 1,6-8,10,25 and 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. (US 6,468,5050B1) as evidenced by VanDeripe (US 5,204,085).

11. Lang et al. (US 6,468,5050B1) teaches of liposomes composed of egg phosphatidylcholine, cholesterol and polyethylene glycol derivatized phosphatidylethanolamine [PEG-PE, i.e. N-(w-methoxypoly(oxyethylene)-α-carbonyl)-1,2-distearyl-3-SH-phosphatidylethanolamine (DSPE)]. The liposomes encapsulate Gd-DTPA-BMA (a nonradioactive contrast agent) and the nonencapsulated materials were removed using sephadex G-50 gel-exclusion chromatography. The liposomes are of the sizes of about 150 nm, 135 nm or 110 nm in mean diameter, are not autoclaved and provided a maximum tumor enhancement after 24 hours. (See column 5, Examples, General Materials and Methods, Preparation of Sterically Stabilized Liposomes Carrying Gd-Chelates for Magnetic Resonance Imaging; figures 1 and 2; column 2, lines 40-49; column 10, lines 37-56). The liposomes of the disclosure can be administered using an intravenous syringe injection, catheter, etc. (column 4, lines 8-22).

12. The liposomes of the disclosure have all of the same constituents (a phospholipid, cholesterol, a phospholipid derivatized with a polymer chain and a nonradioactive contrast-enhancing agent) and are the same size as the liposomes of the instant claims. Therefore, the liposomes of the disclosure anticipate the liposomes of the instant claims, have the same properties and are capable of the same functions, such as enhancing contrast of one or more areas of a subject for X-ray imaging as evidenced by VanDeripe (US 5,204,085). VanDeripe teaches that gadolinium DTPA is

used as an X-ray contrast agent (abstract), thus would meet the limitation of being at least capable of performing the same intended use as claimed.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4,6-11 and 25-33 rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. (US 6,468,5050B1) in view of Klaveness et al. (US 5,676,928) and in further view of Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308).

15. Lang et al. (US 6,468,5050B1) discloses liposomes for computed tomography comprising a phosphatidylcholine (not excluding DPPC), phosphatidylethanolamine, etc. and a poly(ethyleneglycol) is present in the amount of 1 to 25 mole percent of the total lipid content (claims 1-6).

16. For example, the liposomes may be composed of an egg phosphatidylcholine, cholesterol and polyethylene glycol derivatized phosphatidylethanolamine [PEG-PE, i.e. N-(w-methoxypoly(oxyethylene)-α-carbonyl)-1,2-distearyl-3-SH-phosphatidylethanolamine (DSPE)] (molar ratio 3:2:0.3, respectively). The liposomes encapsulate Gd-DTPA-BMA (a nonradioactive contrast agent) and the nonencapsulated materials were removed using sephadex G-50 gel-exclusion chromatography. The liposomes are of the sizes of about 150 nm, 135 nm or 110 nm in mean diameter, are

not autoclaved and provided a maximum tumor enhancement after 24 hours. (See column 5, Examples, General Materials and Methods, Preparation of Sterically Stabilized Liposomes Carrying Gd-Chelates for Magnetic Resonance Imaging; figures 1 and 2; column 2, lines 40-49; column 10, lines 37-56).

17. The liposomes of the disclosure can be administered using an intravenous syringe injection, catheter, etc. and is administered in an amount sufficient to permit selective delivery of the liposome to a tissue where the liposomes selectively target pathologic or cancerous tissues (column 4, lines 8-22; column 2, lines 7-12 and 15-38). The liposomes may further be labeled with antibodies to further enhance targeting (column 4, lines 66+). Lang et al. does not disclose iodinated ionic or iodinated nonionic nonradioactive contrast-enhancing agents or the concentration of such agents.

18. Klaveness et al. (US 5,676,928) discloses liposomes containing at least one imaging agent which is encapsulated within the liposome, including any iodinated X-ray contrast agents (i.e. iodixanol) and heavy metal chelate X-ray contrast agents (i.e. gadolinium (3+)-DTPA-BMA), etc. (column 4, lines 44+; column 5, lines 1-29). The liposomes have an average particle size of preferably 150 nm to 1000 nm (abstract; column 9, lines 28-35). The concentration of iodinated imaging agents is in the range 10-300 mg of encapsulated iodine per ml composition. Klaveness et al. further teaches that iodinated contrast agent containing liposomes can provide for X-ray attenuations of 47 and 70 HU (column 4, lines 60+; example 20).

19. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the Gd-DTPA-BMA contrast agent of Lang et al. (encapsulated

within the about 150 nm, 135 nm, 110 nm liposomes of Lang et al.) for the iodinated X-ray contrast agents (i.e. iodixanol) of Klaveness et al. as Klaveness et al. categorizes them as equivalent imaging agents/contrast agents which can be encapsulated within liposomes having an average particle size of preferably 150 nm to 1000 nm. The size of the liposomes of Lang et al. are critical as those having a mean diameter of 180 nm may not accumulate in a solid tumor, preferably liposomes with a mean diameter of 140 nm accumulate in the periphery of the same solid tumor, and preferably liposomes with a mean diameter of 110 nm accumulate in the peripheral and central portions of that solid tumor (Lang et al. column 4, lines 43-53). Therefore it would have been advantageous to generate liposomes with a mean diameter of 140 nm or 110 nm for accumulation of the liposomes within a solid tumor.

20. In regards to the instant claim 32, Lang et al. teaches that a PEGylated phospholipid is present in the amount of 1 to 25 mole percent of the total lipid content and that the molar ratio of phospholipids, cholesterol and PEGylated phospholipids is 3:2:0.3, respectively. Variations in the amount of PEGylated phospholipid necessarily affects the amount of other liposome constituents and therefore, it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

21. Lang et al does not disclose a hydrogenated soy phosphatidylcholine phospholipid or of the enhanced contrast of at least 50 Houndsfield units.

22. Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) discloses a computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG) (p303, last paragraph). The contrast enhancing iodinated liposome compositions of the disclosure are observed immediately after administration up to 60 min with a mean peak enhancement of in the aorta of approximately 90ΔHU (p305, last paragraph; p306, first paragraph).

23. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute egg phosphatidylcholine for an equivalent soy phosphatidylcholine as it is merely the source of phosphatidylcholine that differs and not the structural entity itself. At the time of the invention it would have been obvious to one ordinarily skilled in the art that iodinated contrast agent containing liposomes of the combined references of Lang et al. and Klaveness et al. will provide for an enhanced contrast of at least 50 Houndsfield units as Leike et al. and Klaveness et al. teach that iodinated liposome compositions provide for approximately 90ΔHU and/0r X-ray attenuations of 47 and 70 HU, respectively.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618